REMARKS

I. Status Summary

Claims 1-134 were filed with the application. Claims 1-134 have previously been cancelled and claims 135-157 added. Claim 158 is herein added. Claims 140, 147, and 154 have previously been cancelled. Claims 136-138, 141, 143 and 156 are herein canceled. Thus, claims 135, 139, 142, 144-146, 148-153, 155 and 157-158 are pending and have been examined by the U.S. Patent and Trademark Office (hereinafter "the Patent Office"). Claims 135-139, 142-146, 148-153, and 155-157 presently stand rejected. Claims 135, 139, 142, 144-146, 148-153, 155 and 157 are currently amended.

Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under 35 U.S.C. §101 as allegedly failing to comply with the utility requirement. Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under 35 U.S.C. §112, second paragraph, upon the contention that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under the judicially created doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 1, 2 and 6 of U.S. Patent No. 6,617,114 (hereinafter referred to as "the '114 Patent") to Fowlkes *et al.*

II. Claim Amendments

Claims 135-157 have been amended for purposes of clarification. Support for the amendments to the claims can be found throughout the claims and specification as filed. In addition, specific support for the amendments to claim 135 can be found throughout the claims and specification as filed and, in particular, at pages 36-46 of the specification. Support for the phrase "peptide conformational probes" in claim 135 can be found, in particular, at page 18, lines 9-12; page 23, lines 12-28; and

page 25, lines 15-16, of the specification. Support for addition of the term "ERα/βV" to claim 135 can be found, in particular, at Table 10 and original claim 157. Specific support for the amendments to claims 139-158 can be found, in particular, at original claim 135. Accordingly, no impermissible new matter has been added by these claim amendments.

III. Response to the Rejections under 35 U.S.C. § 101

Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under 35 U.S.C. §101 as allegedly failing to comply with the utility requirement. Applicants respectfully disagree with the § 101 rejection. For example, a substantial utility is recited in independent claim 135 in a method of predicting the receptor-modulating activity of a test compound when bound to an estrogen receptor. Claim 135 recites a method comprising the steps as follows: contacting an estrogen receptor with a plurality of reference compounds, wherein the reference compound-bound estrogen receptor forms a reference conformation; contacting the reference conformations with a plurality of peptide conformational probes; measuring the binding of the probes to the reference conformations to obtain a fingerprint of the reference compounds; contacting the estrogen receptor with a test compound, wherein the binding of the test compound to the estrogen receptor forms a test conformation; contacting the test conformation with the conformational probes; measuring the binding of the probes to the test conformation and comparing the binding pattern of the probes to the fingerprints of the reference compounds to predict the receptor-modulating activity of the test compound.

The Patent Office appears to be contending that the claimed process of predicting the estrogen receptor modulating activity of a compound has not been fully developed and that the specification provides only prophetic statements. *See Official Action*, page 3. Applicants disagree with this contention. The numerous Examples and significant data provided in the specification describe the identification of numerous peptide conformational probes that exhibit differential binding to estrogen

receptor in unliganded form versus the form of the receptor when bound to a number of known ligands (referred to in the specification as reference compounds). The specification further describes, including the provision of experimental binding data, the use of these peptide conformational probes to fingerprint the binding of the numerous ligands having known biological activity. In this manner the biological activity of a newly discovered ligand can be predicted by probing the receptor conformation when bound to the newly discovered ligand and comparing the probe binding pattern to that for the known ligands.

The ability to probe the conformation of a nuclear receptor, such as the estrogen receptor, by using the peptide conformational probes provided in the instant specification provides valuable information given that the biological function of nuclear receptors is dictated by receptor conformation. The importance of nuclear receptor conformation to biological activity is stated in the specification, for example, at page 4, page 8 (bottom) to page 9 (top), and page 18. In addition, Applicants provide further evidence of the substantial utility of the claimed methods for predicting nuclear receptor-modulating activity of test compounds by way of 20 journal articles describing the relationship between nuclear receptor conformation and biological activity. *See* **Exhibits A-T**. By way of a particular example, Exhibits A and B describe the use of peptide conformational probes to predict the receptor modulating activity of newly identified estrogen receptor ligands according to the method of current claim 1 of the instant application.

Accordingly, applicants respectfully submit that the claimed methods of the instant application have substantial patentable utility and, therefore, respectfully request that the rejection of claims 135-139, 142-146, 148-153, and 155-157 under 35 U.S.C. §101 be withdrawn.

IV. Response to the Rejections under 35 U.S.C. §112, First Paragraph

Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description

requirement. Applicants respectfully traverse the rejection and submit the following remarks.

In response to the rejection under 35 U.S.C. §112, first paragraph, applicants submit herewith a 37 C.F.R. § 1.132 Declaration that includes two publications (Exhibits A & B) describing characterization of the unique conformational changes induced in the estrogen receptor by two newly identified anti-estrogen compounds as disclosed in the instant application. Exhibit A is a true and accurate hard copy of a paper by Connor *et al.* for which a co-inventor, Donald P. McDonnell, is a coauthor and senior author, The Connor *et al.* reference was published in Cancer Research on April 1, 2001 (Connor *et al.*, (2001) *Cancer Research*, 61:2917-22; hereinafter "*Connor et al.*") and describes characterization of a unique conformational change induced in the estrogen receptor by the anti-estrogen compound GW5638. As described in *Connor et al.*, tumor explants that are resistant to the breast cancer therapeutic, tamoxifen, are not cross-resistant to GW5638. The results described in *Connor et al.* indicate that the lack of cross-resistance observed for GW5638 is due to the unique conformational change induced in the estrogen receptor by GW5638 that is not induced by binding of tamoxifen. The general procedures for using peptide conformational probes to determine the estrogen receptor conformational changes induced by tamoxifen and GW5638 as described in *Connor et al.* are disclosed in the subject above-referenced patent application, for example, at Examples 1-5, pages 130-159. Thus, the receptor-modulating activity of the test compound GW5638, when bound to an estrogen receptor, was predicted to be different from that of reference compound tamoxifen, according to the method of current claim 1 of the subject above-referenced patent application.

Similar to Exhibit A, Exhibit B is a true and accurate hard copy of a paper by DuSell *et al.* for which co-inventor, Donald P. McDonnell, is a coauthor and senior author, and which was published in Molecular Endocrinology in 2008 (DuSell *et al.*, (2008) *Molecular Endocrinology*, 22(1):65-77; hereinafter "*DuSell et al.*"). *DuSell et al.* describes characterization of a unique conformational change induced in the

estrogen receptor by the anti-estrogen compound 27-hydroxycholiesterol (27HC). As described in *DuSell et al.*, 27HC induces a unique conformational change in both ERα and ERβ, distinguishing it from other selective estrogen receptor modulators (SERMs) whose relative agonist/antagonist activities vary in a cell- and promoter-dependent manner. The general procedures for using peptide conformational probes to determine the estrogen receptor conformational changes induced by 27HC and other SERMs as described in *DuSell et al.* are disclosed in the subject above-referenced patent application, for example, at Examples 1-5, pages 130-159. Thus, the receptor-modulating activity of the test compound 27HC, when bound to an estrogen receptor, was predicted to be different from that of reference compound estradiol (E2), according to the method of current claim 1 of the subject above-referenced patent application.

In light of the foregoing remarks and Declaration pursuant to 37 C.F.R. § 1.132, applicants respectfully request that the instant 35 U.S.C. §112, first paragraph, rejection of claims 135-139, 142-146, 148-153, and 155-157 be withdrawn at this time.

V. Response to the Rejections under 35 U.S.C. §112, Second Paragraph

Claims 135-139, 142-146, 148-153, and 155-157 have been rejected under 35 U.S.C. §112, second paragraph, upon the contention that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. While Applicants disagree with this rejection, claims 135-157 have been amended to facilitate prosecution of the instant application. In particular, claim 135 has been amended at part (c) by addition of the phrase "peptide conformational probes" for purposes of enhancing the ease of understanding of the claims. Additional amendments have been made throughout the pending claims for purposes of clarification. Claim 136, which had contained the phrase "panel-based descriptor" has been canceled. Therefore, Applicants respectfully assert that current claims 135-139, 142-146, 148-153, and 155-157 are not indefinite.

Accordingly, Applicants respectfully request that the instant 35 U.S.C. §112, second paragraph, rejection of claims 135-139, 142-146, 148-153, and 155-157 be withdrawn at this time.

VI. Response to the Obviousness-Type Double Patenting Rejection

Claims 135-139, 142-146, 148-153, and 155-157 presently stand rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, and 6 of the '114 Patent. Applicants respectfully traverse the rejection and submit the following remarks.

In contrast to Applicants current claim 135, claims 1, 2, and 6 of the '114 Patent are directed to identifying a ligand *which inhibits the binding of an estrogen receptor to a binding partner ligand.* Claim 1 of the '114 Patent recites a screening step to identify the ligand having the ability to inhibit the binding of the binding partner ligand to the estrogen receptor. In contrast, Applicants' claim 135 is directed to predicting the receptor modulating activity of a test compound through the use of peptide conformational probes rather than identifying an inhibitor of receptor-ligand binding. Claims 1, 2, and 6 of the '114 Patent fail to teach or suggest the use of such peptide conformational probes. Therefore, Applicants respectfully submit that claims 1, 2, and 6 of the '114 Patent fail to render the currently pending claims of the instant application obvious.

Accordingly, Applicants respectfully request that the instant rejection of claims 135-139, 142-146, 148-153, and 155-157 under the judicially created doctrine of obviousness-type double patenting be withdrawn at this time.

CONCLUSION

In light of the above amendments and remarks, it is respectfully submitted that the present application is now in proper condition for allowance, and an early notice to such effect is earnestly solicited.

If any small matter should remain outstanding after the Patent Examiner has had an opportunity to review the above amendments and remarks, the Patent Examiner is respectfully requested to telephone the undersigned patent attorney in order to resolve these matters and avoid the issuance of another Official Action.

Any fees due with this Reply may be charged to Deposit Account **23-1665** under Customer Number **27267**.

Respectfully submitted,

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